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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/709,170	11/10/2000	Raymond P. Warrell	10412-025	4982

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/709,170	WARRELL ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23 and 29-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23 and 29-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission mailed on December 23, 2005 has been entered.

Claims 1 and 19 have been amended. Claims 1-23 and 29-33 are pending in the instant application.

Claims 1-23 and 29-33 have been examined on the merits.

Response to Arguments

Applicants Amendment and Response mailed December 23, 2005 have been considered. Rejections and/or objections not reiterated from the previous office action mailed July 13, 2005 are hereby withdrawn. Any arguments addressing said rejections and/or objections are moot. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Claim Rejections - 35 USC § 102 or 35 USC § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5 and 13-18 are rejected under 35 U.S.C. 102(b) or 103(a) as being anticipated by or obvious over Webb et al. (The Lancet, 1997 Vol. 349:1137-1141).

Claims 1-5 and 13-17 are drawn to a method of treating cancer in a human comprising administering a bcl-2 antisense in one or more cycles of therapy, each cycle of therapy consisting of 2 to 13 days. Claim 18 is drawn to a specific bcl-2 antisense oligonucleotide, SEQ ID NO:17.

Webb et al. disclose bcl-2 antisense therapy in patients with non-Hodgkin lymphoma (see Abstract). Webb et al. disclose the reduction of bcl-2 protein levels in the lymph node aspirates of patient 6 after the 7-day administration of a fully phosphorothioated bcl-2 antisense oligonucleotide (see Figure 2). It is noted that the bcl-2 antisense oligonucleotide disclosed by Webb et al. is 100% identical to SEQ ID NO:17 of the instant invention. Webb et al. are silent regarding the treatment of cancer

at day 7 in patient 6. However, since the instant claims are simply drawn to a method of treating cancer in a human comprising one step, namely the administration of a bcl-2 antisense for less than 14 days, and Webb et al. disclose the 7-day administration of a bcl-2 antisense oligonucleotide in patient 6 at Figure 2, it is the Examiner's position that at day 7, the cancer in patient 6 was inherently treated since the method disclosed by Webb et al. is fully embraced in the method as instantly claimed.

Response to Arguments

A similar rejection was maintained in the previous Office Action mailed July 13, 2005. In response to this rejection, Applicants argue that Webb et al. teach at page 1138, second full paragraph:

> "... one 2-week course of treatment was given. Patients were followed up for 4 weeks after the end of treatment. If there was evidence of tumor response, a second course of treatment was given."

Applicants also argue that the instant specification at page 7, lines 1-6 discloses:

> "As used herein, the phrases "treating cancer" and "treatment of cancer" means to inhibit the replication of cancer cells, inhibit the spread of cancer, decrease tumor size, lessen or reduce the number of cancerous cells in the body, or ameliorate or alleviate the symptoms of the disease caused by the cancer. The treatment is considered therapeutic if there is a decrease in mortality and/or mortality and /or morbidity, or a decreased in disease burden manifest by reduced numbers of malignant cells in the body."

Applicants argue that the Examiner's reliance on the reduction of bcl-2 levels after 7 days of administration of bcl-2 antisense as evidence of "treatment/therapy" is misplaced since bcl-2 levels are not considered to be evidence of treatment. Applicants argue that Webb et al. only evaluate the tumor response 4 weeks after bcl-2 antisense

administration is completed. Applicants contend that the instant claims are drawn to a method for treating cancer in which a 2-13 day course of therapy is employed and Webb et al. neither teaches nor suggest that anything less than 14 days of administration is effective to treat cancer.

Applicant's arguments have been fully considered, but are not found persuasive. First off, the Examiner has revisited the instant specification at page 7, lines 1-6, which discloses the definition of the phrases "treating cancer" and "treatment of cancer". Second, the Examiner agrees with Applicant that Webb et al. disclose at page 1138, second full paragraph: "... one 2-week course of treatment was given". Finally, the Examiner also agrees with Applicant that the the instant claims are drawn to a method for treating cancer in which a 2-13 day couse of therapy of bcl-2 antisense is employed.

It is clear that Webb et al. evaluate the tumor response 4 weeks after bcl-2 antisense administration is complete (see page 1138, second full paragraph). However, Webb et al. teach a 7 day couse of therapy of bcl-2 antisense was administered to patient 6, in which Bcl-2 levels were reduced in lymph node aspirates (see Figure 2). It is noted that Webb et al. are silent regarding "treatment of cancer" at day 7 in patient 6. However, it is the Examiner's position that at day 7, the cancer in patient 6 was inherently treated since the method disclosed by Webb et al. is fully encompassed in the methods as instantly claimed. (e.g. the instant climas are drawn to treating cancer in a patient following a course of bcl-2 antisense therapy for less than 14 days and Webb et al. teach administering to patient 6, a bcl-2 antisense for 7 days, which is less than 14 days).

For further explantation, see MPEP § 2112, which states "[w]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim, but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. 'There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102.' *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims".

In summary, the instant claims are simply drawn to a method of treating cancer in a human comprising one step, namely the administration of a bcl-2 antisense for less than 14 days. Webb et al. disclose the reduction of bcl-2 protein levels in the lymph node aspirates of patient 6 after a 7-day administration of a bcl-2 antisense oligonucleotide. Since Webb et al. teach the one step recited in the instant method, it is the Examiner's position that at day 7, the cancer in patient 6 would be treated inherently since the method disclosed by Webb et al. is fully embraced in the methods as instantly claimed.

The Examiner would like to point out that She is not arguing that a reduction in bcl-2 levels is considered to be evidence of cancer treatment. Instead, the Examiner is arguing that since Webb et al. teach the only method step recited in the instant claims,

the method disclosed by Webb et al. would inherently "treat cancer" as defined in the instant specification at page 7, lines 1-6.

Claims 1-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al. (The Lancet, 1997 Vol. 349:1137-1141) in view of Bennett et al. [U.S. Patent No: 6,214,986].

Claim 1 is drawn to a method of treating cancer in a human comprising administering a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg daily in one or more cycles of therapy, each cycle of therapy consisting of 2 to 13 days. Claims 2-17 are dependent on claim 1 and include all the limitations of claim 1, with the further limitations wherein one or more cycles of therapy consist of 3 to 9 days; wherein one or more cycles of therapy consist of 4 to 7 days; wherein the bcl-2 antisense oligonucleotide is administered at a dose of 4 to 9 mg/kg/day; wherein the bcl-2 antisense oligonucleotide is administered at a dose of 5 to 7 mg/kg/day; and further comprises administering one or more cancer therapeutics. Claim 18 is drawn to a specific bcl-2 antisense oligonucleotide, SEQ ID NO:17. Claim 19 is drawn to a method of treating or preventing cancer in a human comprising administering one or more chemoagents and a bcl-2 antisense oligonucleotide, wherein the bcl-2 antisense oligonucleotide is administered at a dose of 0.01 to 50 mg/kg daily in one or more cycles of therapy, each cycle of therapy consisting of 2 to 13 days. Claims 20-23 are dependent on claim 19 and include all the limitations of claim 19, with the further limitations of specific chemoagents, and specific doses of chemoagents.

Webb et al. teach bcl-2 antisense therapy in patients with non-Hodgkin lymphoma (see Abstract). Webb et al. teach the reduction of bcl-2 protein levels in the lymph node aspirates of patient 6 after the 7-day administration of a fully phosphorothioated bcl-2 antisense oligonucleotide (see Figure 2). It is noted that the bcl-2 antisense oligonucleotide disclosed by Webb et al. is 100% identical to SEQ ID NO:17 of the instant invention. Webb et al. are silent regarding the treatment of cancer at day 7 in patient 6. However, since the instant claims are simply drawn to a method of treating cancer in a human comprising one step, namely the administration of a bcl-2 antisense for less than 14 days, and Webb et al. teach the 7-day administration of a bcl-2 antisense oligonucleotide in patient 6 at Figure 2, it is the Examiner's position that at day 7, the cancer in patient 6 was inherently treated since the method taught by Webb et al. is fully embraced in the method as instantly claimed. (e.g. the instant climas are drawn to treating cancer in a patient following a course of bcl-2 antisense therapy for less than 14 days and Webb et al. teach administering to patient 6, a bcl-2 antisense for 7 days, which is less than 14 days).

Webb et al. do not teach further administering an antisense oligonucleotide with one or more cancer therapeutics at specific doses.

Bennett et al. teach the antisense modulation of bcl expression using therapeutic compositions comprising antisense nucleic acids. Bennett et al. also teach bcl antisense oligonucleotides are administered with one or more cancer therapeutics, including doxorubicin, 5-fluorouracil (5-FU), etoposide, and cisplatin, for example (see column 16, lines 28-52). Bennett et al. also teach bcl antisense oligonucleotides are

administered with prodrugs (see columns 11 and 12, last and first paragraphs, respectively). Bennett et al. teach "the formulation of therapeutic compositions and their subsequent administration is believed to be within the skill of those in the art. Dosing is dependent on severity and responsiveness of the disease state to be treated, with the course of treatment lasting from several days to several months, or until a cure is effected or a diminution of the disease state is achieved. Optimal dosing schedules can be calculated from measurements of drug accumulation in the body of the patient. Persons of ordinary skill can easily determine optimum dosages, dosing methodologies and repetition rates. Optimum dosages may vary depending on the relative potency of individual oligonucleotides, and can generally be estimated based on EC_{50s} found to be effective in *in vitro* and *in vivo* animal models. In general, dosage is from 0.01 μg to 100 g per kg of body weight, and may be given once or more daily, weekly, monthly or yearly, or even once every 2 to 20 years. Persons of ordinary skill in the art can easily estimate repetition rates for dosing based on measure residence times and concentrations of the drug in bodily fluids or tissues" (see columns 16-17, last and first paragraphs, respectively).

It would have been obvious to one of ordinary skill in the art to devise a method of treating cancer in a human comprising administering a bcl-2 antisense oligonucleotide in one or more cycles of therapy, each cycle of therapy consisting of 2 to 13 days as taught by Webb et al. for the purpose of treating non-Hodgkin lymphoma. One of ordinary skill in the art would have been motivated to vary the cycles of therapy or to vary the therapeutic composition dosage amount since it is routine and well known

in the art to determine optimum dosages, dosing methodologies, and repetition rates based on measured residence times and concentrations of the drug in bodily fluids or tissues as taught by Bennett et al. One of ordinary skill in the art would have been motivated and expected success in administering the antisense therapy with one or more cancer therapeutics or chemoagents since it is routine and well known in the art that combination therapy is an effective approach for cancer treatment as taught by Bennett et al.

Therefore, the invention of claims 1-23 would have been *prima facie* obvious to one of ordinary skill in the art, as a whole, at the time the instant invention was made.

Response to Arguments

A similar rejection was maintained in the previous Office Action mailed July 13, 2005. In response to this rejection, Applicants argue that Webb et al. fail to teach or suggest treatment of cancer as defined in the specification with less than a 14-day administration of bcl-2 antisense.

This argument has been fully considered, but is not found persuasive because Webb et al. teach bcl-2 antisense therapy in patients with non-Hodgkin lymphoma (see Abstract). Webb et al. teach the reduction of bcl-2 protein levels in the lymph node aspirates of patient 6 after the 7-day administration of a fully phosphorothioated bcl-2 antisense oligonucleotide (see Figure 2). Webb et al. are silent regarding the "treatment of cancer" at day 7 in patient 6. However, since the instant claims are simply drawn to a method of treating cancer in a human comprising one step, namely the administration of

a bcl-2 antisense for less than 14 days, and Webb et al. teach the 7-day administration of a bcl-2 antisense oligonucleotide in patient 6 at Figure 2, it is the Examiner's position that at day 7, the cancer in patient 6 was inherently treated since the method taught by Webb et al. is fully emcompassed in the method as instantly claimed.

Claims 29-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al., (The Lancet, 1997 Vol. 349:1137-1141) in view of Bennett et al. [U.S. Patent No: 6,214,986].

Claims 29 and 30 are drawn to a pharmaceutical composition comprising a bcl-2 antisense oligonucleotide for administration for one or more cycles of therapy, each cycle consisting of 2 to 13 days, in combination with a cancer therapeutic agent, wherein the dose of the bcl-2 antisense is 0.01 to 50 mg/kg/day or 10 to 50 mg/kg/day, respectively. Claims 31 and 32 are dependent on either claim 29 or 30, and include all the limitations of claim 29 or 30, with the further limitations, wherein the pharmaceutical composition is form 10 to 40 bases in length and is complementary to the bcl-2 gene; and wherein the antisense oligonucleotide comprises at least two phosphorothioate linkages. Claim 33 is drawn to a specific bcl-2 antisense oligonucleotide, SEQ ID NO:17.

Webb et al. teach bcl-2 antisense therapy in patients with non-Hodgkin lymphoma (see Abstract). Webb et al. teach the reduction of bcl-2 protein levels in the lymph node aspirates of patient 6 after the 7-day administration of a fully phosphorothioated bcl-2 antisense oligonucleotide (see Figure 2). It is noted that the

bcl-2 antisense oligonucleotide disclosed by Webb et al. is 100% identical to SEQ ID NO:17 of the instant invention. Webb et al. are silent regarding the treatment of cancer at day 7 in patient 6. However, since the instant claims are simply drawn to a method of treating cancer in a human comprising one step, namely the administration of a bcl-2 antisense for less than 14 days, and Webb et al. teach the 7-day administration of a bcl-2 antisense oligonucleotide in patient 6 at Figure 2, it is the Examiner's position that at day 7, the cancer in patient 6 was inherently treated since the method taught by Webb et al. is fully embraced in the method as instantly claimed. (e.g. the instant climas are drawn to treating cancer in a patient following a course of bcl-2 antisense therapy for less than 14 days and Webb et al. teach administering to patient 6, a bcl-2 antisense for 7 days, which is less than 14 days).

Webb et al. do not teach further administering an antisense oligonucleotide with one or more cancer therapeutics at specific doses.

Bennett et al. teach the antisense modulation of bcl expression using therapeutic compositions comprising antisense nucleic acids. Bennett et al. also teach bcl antisense oligonucleotides are administered with one or more cancer therapeutics, including doxorubicin, 5-fluorouracil (5-FU), etoposide, and cisplatin, for example (see column 16, lines 28-52). Bennett et al. also teach bcl antisense oligonucleotides are administered with prodrugs (see columns 11 and 12, last and first paragraphs, respectively). Bennett et al. teach "the formulation of therapeutic compositions and their subsequent administration is believed to be within the skill of those in the art. Dosing is dependent on severity and responsiveness of the disease state to be treated, with the

course of treatment lasting from several days to several months, or until a cure is effected or a diminution of the disease state is achieved. Optimal dosing schedules can be calculated from measurements of drug accumulation in the body of the patient. Persons of ordinary skill can easily determine optimum dosages, dosing methodologies and repetition rates. Optimum dosages may vary depending on the relative potency of individual oligonucleotides, and can generally be estimated based on EC_{50s} found to be effective in *in vitro* and *in vivo* animal models. In general, dosage is from 0.01 μg to 100 g per kg of body weight, and may be given once or more daily, weekly, monthly or yearly, or even once every 2 to 20 years. Persons of ordinary skill in the art can easily estimate repetition rates for dosing based on measure residence times and concentrations of the drug in bodily fluids or tissues" (see columns 16-17, last and first paragraphs, respectively).

It would have been obvious to one of ordinary skill in the art to devise a pharmaceutical composition comprising a bcl-2 antisense oligonucleotide for administration for one or more cycles of therapy, each cycle of therapy consisting of 2 to 13 days as taught by Webb et al. for the purpose of treating non-Hodgkin lymphoma. One of ordinary skill in the art would have been motivated to vary the cycles of therapy or to vary the therapeutic composition dosage amount since it is routine and well known in the art to determine optimum dosages, dosing methodologies, and repetition rates based on measured residence times and concentrations of the drug in bodily fluids or tissues as taught by Bennett et al. One of ordinary skill in the art would have been motivated and expected success in administering the antisense therapy with one or

more cancer therapeutics or chemoagents since it is routine and well known in the art that combination therapy is an effective approach for cancer treatment as taught by Bennett et al.

Therefore, the invention of claims 29-33 would have been *prima facie* obvious to one of ordinary skill in the art, as a whole, at the time the instant invention was made.

Response to Arguments

A similar rejection was maintained in the previous Office Action mailed July 13, 2005. In response to this rejection, Applicants argue that Webb et al. fail to teach or suggest treatment of cancer as defined in the specification with less than a 14-day administration of bcl-2 antisense.

This argument has been fully considered, but is not found persuasive because Webb et al. teach bcl-2 antisense therapy in patients with non-Hodgkin lymphoma (see Abstract). Webb et al. teach the reduction of bcl-2 protein levels in the lymph node aspirates of patient 6 after the 7-day administration of a fully phosphorothioated bcl-2 antisense oligonucleotide (see Figure 2). Webb et al. are silent regarding the "treatment of cancer" at day 7 in patient 6. However, since the instant claims are simply drawn to a method of treating cancer in a human comprising one step, namely the administration of a bcl-2 antisense for less than 14 days, and Webb et al. teach the 7-day administration of a bcl-2 antisense oligonucleotide in patient 6 at Figure 2, it is the Examiner's position that at day 7, the cancer in patient 6 was inherently treated since the method taught by Webb et al. is fully encompassed in the method as instantly claimed.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
January 12, 2006

SEAN McGARRY
PRIMARY EXAMINER
1635